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#3

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :

A61K 37/02

A1

(11) International Publication Number:

WO 94/28923

(43) International Publication Date: 22 December 1994 (22.12.94)

(21) International Application Number: PCT/US94/06418

(22) International Filing Date: 7 June 1994 (07.06.94)

(30) Priority Data:  
08/075,032 10 June 1993 (10.06.93) US

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(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN,  
CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU,  
LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD,  
SE, SK, UA, UZ, VN, European patent (AT, BE, CH, DE,  
DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI  
patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE,  
SN, TD, TG).

Published

*With international search report.*

*Before the expiration of the time limit for amending the  
claims and to be republished in the event of the receipt of  
amendments.*

(54) Title: MULTIPLE BOTULINUM TOXINS FOR TREATING NEUROMUSCULAR DISORDERS AND CONDITIONS

(57) Abstract

A method and composition for treating a patient suffering from a neuromuscular disorder or condition include the administration to the patient of a therapeutically effective amount of a combination of at least two neurotoxins selected from a group consisting of botulinum toxin types A, B, C, D, E, F and G. The amount of each selected neurotoxin administered is further selected to control a duration of therapeutic activity of the administered combination.

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MULTIPLE BOTULINUM TOXINS FOR TREATING NEUROMUSCULAR  
DISORDERS AND CONDITIONS

5      FIELD OF THE INVENTION

10      The present invention provides novel methods and composition for treating diseases of the nervous system, e.g., neuromuscular disorders and conditions, with botulinum toxins. In addition, the present invention provides methods useful in all tissue and organ systems which involve the release of neurotransmitters, especially acetylcholine. These cholinergic transmission systems include neuromuscular  
15      junctions (muscles), smooth muscles (gut, sphincters, etc.) and secretions (salivation and mucus).

BACKGROUND OF THE INVENTION

20      A bacterial toxin, botulinum toxin, in particular botulinum toxin type A, has been used in the treatment of a number of neuromuscular disorders and conditions involving muscular spasm; for example, strabismus, blepharospasm, spasmodic torticollis (cervical  
25      dystonia), oromandibular dystonia and spasmodic dysphonia (laryngeal dystonia). The toxin binds rapidly and strongly to presynaptic cholinergic nerve terminals and inhibits the exocytosis of acetylcholine by decreasing the frequency of acetylcholine release.  
30      This results in local paralysis and hence relaxation of the muscle afflicted by spasm.

For one example of treating neuromuscular disorders, see U.S. Patent No. 5,053,005 to Borodic,  
35      which suggests treating curvature of the juvenile

spine, i.e., scoliosis, with an acetylcholine release inhibitor, preferably botulinum toxin A.

5 For the treatment of strabismus with botulinum toxin type A, see Elston, J.S., et al., *British Journal of Ophthalmology*, 1985, 69, 718-724 and 891-896. For the treatment of blepharospasm with botulinum toxin type A, see Adenis, J.P., et al., *J. Fr. Ophthalmol.*, 1990, 13 (5) at pages 259-264.  
10 For treating squint, see Elston, J.S., *Eye*, 1990, 4(4):VII. For treating spasmodic and oromandibular dystonia torticollis, see Jankovic et al., *Neurology*, 1987, 37, 616-623.

15 Spasmodic dysphonia has been treated with botulinum toxin type A. See Blitzner et al., *Ann. Otol. Rhino. Laryngol*, 1985, 94, 591-594. Lingual dystonia was treated with botulinum toxin type A according to Brin et al., *Adv. Neurol.* (1987) 50, 599-  
20 608. Finally, Cohen et al., *Neurology* (1987) 37 (Suppl. 1), 123-4, discloses the treatment of writer's cramp with botulinum toxin type A.

25 The term botulinum toxin is a generic term embracing the family of toxins produced by the anaerobic bacterium *Clostridium botulinum* and, to date, seven immunologically distinct neurotoxins have been identified. These have been given the designations A, B, C, D, E, F and G. For further information concerning the properties of the various botulinum  
30 toxins, reference is made to the article by Jankovic and Brin, *The New England Journal of Medicine*, No. 17, 1990, pp. 1186-1194, and to the review by Charles L. Hatheway in Chapter 1 of the book entitled *Botulinum Neurotoxin and Tetanus Toxin*, L. L. Simpson, Ed.,  
35

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published by Academic Press Inc. of San Diego, California, 1989, the disclosures in which are incorporated herein by reference.

5           The neurotoxic component of botulinum toxin has  
a molecular weight of about 150 kilodaltons and is  
thought to comprise a short polypeptide chain of about  
50 kD which is considered to be responsible for the  
toxic properties of the toxin, i.e., by interfering  
10       with the exocytosis of acetylcholine, by decreasing  
the frequency of acetylcholine release, and a larger  
polypeptide chain of about 100 kD which is believed to  
be necessary to enable the toxin to bind to the pre-  
synaptic membrane. The "short" and "long" chains are  
15       linked together by means of a simple disulfid bridge.  
(It is noted that certain serotypes of botulinum  
toxin, e.g., type E, may exist in the form of a single  
chain un-nicked protein, as opposed to a dichain. The  
single chain form is less active but may be converted  
20       to the corresponding dichain by nicking with a  
protease, e.g., trypsin. Both the single and the  
dichain are useful in the method of the present  
invention.)

25           Immunotoxin conjugates of ricin and antibodies,  
which are characterized as having enhanced cytotoxi-  
city through improving cell surface affinity, are  
disclosed in European Patent Specification 0 129 434.  
The inventors note that botulinum may be utilized in  
30       place of ricin.

          Botulinum toxin is obtained commercially by  
establishing and growing cultures of *C. botulinum* in  
a fermenter and then harvesting and purifying the  
35       fermented mixture in accordance with known techniques.

Botulinum toxin type A, the toxin type generally utilized in treating neuromuscular conditions, is currently available commercially from several sources; for example, from Port Products Ltd. UK, under the trade name "DYSPORT," and from Allergan, Inc., Irvine, California, under the trade name BOTOX®.

It is one object of the invention to provide novel treatments of neuromuscular disorders and conditions with botulinum toxin type A in combination with botulinum toxin types B, C, D, E, F and G.

#### SUMMARY OF THE INVENTION

The present invention provides a composition and a method of treating a neuromuscular disorder or condition such as strabismus and other disorders of ocular motility, e.g., comitant and vertical strabismus, lateral rectus palsy, nystagmus, dysthyroid myopathy, etc.; dystonia, e.g., focal dystonias such as spasmodic torticollis, writer's cramp, blepharospasm, oromandibular dystonia and the symptoms thereof, e.g., bruxism, Wilson's disease, tardive dystonia, laryngeal dystonia etc.; other dystonias, e.g., tremor, tics, segmental myoclonus; spasms, such as spasticity due to chronic multiple sclerosis, spasticity resulting in abnormal bladder control, e.g., in patients with spinal cord injury, animus, back spasm, charley horse etc.; tension headaches; levator pelvic syndrome; spina bifida, tardive dyskinesia; Parkinson's and limb (focal) dystonia and stuttering, etc. of a patient, which method comprises administering to the patient suffering from said disorder or condition a therapeutically effective amount of botulinum toxin

type A in combination with a neurotoxin selected from the group consisting of botulinum toxin types B, C, D, E, F and G. The clinical features of the above-listed neuromuscular disorders and conditions are described  
5 in Jankovic and Brin, cited above, and in Quinn, *Disorders of Movement*, Academic Press, 1989, all of which are incorporated herein by reference.

The present invention further provides  
10 compositions of said botulinum toxins in a vehicle suitable for injection of said toxins into the appropriate region of the patient to be treated. Alterations of the vehicle and excipient may include materials designed to retain the injected toxin in the  
15 local area.

The present invention further provides a composition and a method for treating neuromuscular disorders or conditions requiring a short duration of  
20 therapeutic action (measured in hours or days) or an intermediate duration of therapeutic action (measured in weeks). For example, a short or intermediate duration neurotoxin may be used in procedures to temporarily immobilize a joint or prevent muscle  
25 contractions prior to or after surgery or a procedure. Examples of these conditions include: total joint replacement, treatment of compound fractures, joint infections, dislocations. Other uses of a short duration of action product are to aid in joint  
30 dislocations, relaxation for physical therapy, alleviation of muscle spasms (to break the cycle of pain and spasm). In addition, a short duration therapy may be useful to determine the muscles involved in curvature of the spine in scoliosis.  
35 Unusual spasms of sphincter muscles (ocular,

gastrointestinal, vaginal, etc.) may be treated with short duration therapy.

5 On the other hand, an intermediate duration product may be useful in treating tendon or ligament alignment repair. If a muscle is damaged after trauma, immobilization with an intermediate may help with pain and facilitate healing. In addition, an intermediate duration therapy may be useful in  
10 determination of muscles involved in curvature of the spine in scoliosis. Unusual spasms of sphincter muscles (ocular, gastrointestinal, vaginal, etc.) may be treated with intermediate duration therapy.

15 DETAILED DESCRIPTION

The botulinum toxins used according to the present invention are botulinum toxins type A, B, C, D, E, F and G.

20

Each serotype of botulinum toxin has been identified as immunologically different proteins through the use of specific antibodies. For example, if the antibody (antitoxin) recognizes, that is,  
25 neutralizes the biological activity of, for example, type A it will not recognize types B, C, D, E, F or G.

While all of the botulinum toxins appear to be zinc endopeptidases, the mechanism of action of  
30 different serotypes, for example, A and E within the neuron appear to be different than that of type B. In addition, the neuronal surface "receptor" for the toxin appears to be different for the serotypes.



The physiologic groups of *Clostridium botulinum* types are listed in Table I.

Table I. Physiologic Groups of *Clostridium botulinum*

Group	Toxin Sero-Type	Biochemistry	Milk Digest	Glucose Fermentation	Lipase	Phages & Plasmids	Phenotypically Related <i>Clostridium</i> (nontoxigenic)
I	A,B,F	proteolytic saccharolytic	+	+	+	+	<u><i>C. sporogenes</i></u>
II	B,E,F	nonproteolytic saccharolytic psychotrophic	-	+	+	+	
III	C,D	nonproteolytic saccharolytic	+	+	+	+	<u><i>C. novyi</i></u>
IV	G	proteolytic nonsaccharolytic	+	-	-	-	<u><i>C. subterminale</i></u>

These toxin types may be produced by selection from the appropriate physiologic group of *Clostridium botulinum* organisms. the organisms designated as Group I are usually referred to as proteolytic and produce botulinum toxins of types A, B and F. The organisms designated as Group II are saccharolytic and produce botulinum toxins of types B, E and F. The organisms designated as Group III produce only botulinum toxin types C and D and are distinguished from organisms of Groups I and II by the production of significant amounts of propionic acid. Group IV organisms only produce neurotoxin of type G. The production of any and all of the botulinum toxin types A, B, C, D, E, F and G are described in Chapter 1 of *Botulinum Neurotoxin and Tetanus Toxin*, cited above, and/or the references cited therein. Botulinum toxins types B, C, D, E, F and G are also available from various species of clostridia. Currently fourteen species of clostridia are considered pathogenic. Most of the pathogenic strains produce toxins which are responsible for the various pathological signs and symptoms. Organisms which produce botulinum toxins have been isolated from botulism outbreaks in humans

(types A, B, E and F) and animals (types C and D). Their identities were described through the use of specific antitoxins (antibodies) developed against the earlier toxins. Type G toxin was found in soil and has low toxigenicity. However, it has been isolated from autopsy specimens, but thus far there has not been adequate evidence that type G botulism has occurred in humans.

In general, four physiologic groups of *C. botulinum* are recognized (I, II, III, IV). The organisms capable of producing a serologically distinct toxin may come from more than one physiological group. For example, Type B and F toxins can be produced by strains from Group I or II. In addition, other strains of clostridial species (*C. baratii*, type F; *C. butyricum*, type E; *C. novyi*, type C<sub>1</sub> or D) have been identified which can produce botulinum neurotoxins.

Preferably, the toxin is administered by means of intramuscular injection directly into a spastic muscle, in the region of the neuromuscular junction, although alternative types of administration (e.g., subcutaneous injection), which can deliver the toxin directly to the affected muscle region, may be employed where appropriate. The toxin can be presented as a sterile pyrogen-free aqueous solution or dispersion and as a sterile powder for reconstitution into a sterile solution or dispersion.

Where desired, tonicity adjusting agents such as sodium chloride, glycerol and various sugars can be added. Stabilizers such as human serum albumin may also be included. The formulation may be preserved by

means of a suitable pharmaceutically acceptable preservative such as a paraben, although preferably it is unpreserved.

5           It is preferred that the toxin is formulated in unit dosage form; for example, it can be provided as a sterile solution in a vial or as a vial or sachet containing a lyophilized powder for reconstituting a suitable vehicle such as water for injection.

10           In one embodiment, the botulinum toxin is formulated in a solution containing saline and pasteurized human serum albumin, which stabilizes the toxin and minimizes loss through non-specific adsorption. The solution is sterile filtered (0.2 micron filter), filled into individual vials and then vacuum-dried to give a sterile lyophilized powder. In use, the powder can be reconstituted by the addition of sterile unpreserved normal saline (sodium chloride 0.9% for injection).

15           The dose of toxin administered to the patient will depend upon the severity of the condition; e.g., the number of muscle groups requiring treatment, the age and size of the patient and the potency of the toxin. The potency of the toxin is expressed as a multiple of the LD<sub>50</sub> value for the mouse, one unit (U) of toxin being defined as being the equivalent amount of toxin that kills 50% of a group of 18 to 20 female Swiss-Webster mice, weighing about 20 grams each.

20           The dosages used in human therapeutic applications are roughly proportional to the mass of muscle being injected. Typically, the dose administered to the patient may be up to about 1,000 units;

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for example, up to about 500 units, and preferably in the range from about 80 to about 460 units per patient per treatment, although smaller or larger doses may be administered in appropriate circumstances.

5

As the physicians become more familiar with the use of this product, the dose may be changed. In the botulinum toxin type A, available from Porton, DYSPORT, 1 nanogram (ng) contains 40 U. 1 ng of the  
10 botulinum toxin type A, available from Allergan, Inc., i.e., BOTOX®, contains 4 U. The potency of botulinum toxin and its long duration of action mean that doses will tend to be administered on an infrequent basis. Ultimately, however, both the quantity of toxin  
15 administered and the frequency of its administration will be at the discretion of the physician responsible for the treatment and will be commensurate with questions of safety and the effects produced by the toxin.

20

The invention will now be illustrated by reference to the following nonlimiting examples.

In each of the examples, the appropriate muscles  
25 of each patient are injected with a sterile solution containing the confirmation of botulinum toxin. Total patient doses range from 80 U to 460 U. Before injecting any muscle group, careful consideration is given to the anatomy of the muscle group, the aim  
30 being to inject the area with the highest concentration of neuromuscular junctions, if known. Before injecting the muscle, the position of the needle in the muscle is confirmed by putting the muscle through its range of motion and observing the  
35 resultant motion of the needle end. General

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anaesthesia, local anaesthesia and sedation are used according to the age of the patient, the number of sites to be injected, and the particular needs of the patient. More than one injection and/or sites of  
5 injection may be necessary to achieve the desired result. Also, some injections, depending on the muscle to be injected, may require the use of fine, hollow, teflon-coated needles, guided by electromyography.

10 Following injection, it is noted that there are no systemic or local side effects and none of the patients are found to develop extensive local hypotonicity. The majority of patients show an improvement  
15 in function both subjectively and when measured objectively.

#### Example 1

##### The Use of Botulinum Toxin Type in the Treatment 20 of Tardive Dyskinesia

A patient, suffering from joint dislocation, is treated with a composition having up to 500 units of botulinum toxin type A and a lesser amount of botu-  
25 linum toxin type B by direct injection of such toxin into the joint. After several hours, the joint is immobilized and muscle contractions are relieved. An increase, or enhancement, of the relief of muscle enhancement caused by the combination of botulinum  
30 toxin type A and B for a short duration enables immediate treatment while the long term relief of muscle enhancement enables healing of the reset joint.

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Example 1(a)

5 The method of Example 1 is repeated, except that  
a combination of botulinum toxin type A and B is used  
with similar results.

Example 1(b)

10 The method of Example 1 is repeated, except that  
a combination of botulinum toxin type A and C is used  
with similar results.

Example 1(c)

15 The method of Example 1 is repeated, except that  
a combination of botulinum toxin type A and D is used  
with similar results.

Example 1(d)

20 The method of Example 1 is repeated, except that  
a combination of botulinum toxin type A and E is used  
with similar results.

25

Example 1(e)

30 The method of Example 1 is repeated, except that  
a combination of botulinum toxin type A and F is used  
with similar results.

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Example 1(f)

5 The method of Example 1 is repeated, except that a combination of botulinum toxin type A and G is used with similar results.

Example 2Use of Botulinum Toxin in the Treatment  
of Spasmodic Torticollis

10

A patient, suffering from spasmodic torticollis, as manifested by spasmodic or tonic contractions of the neck musculature, producing stereotyped abnormal deviations of the head, the chin being rotated to one side, and the shoulder being elevated toward the side at which the head is rotated, is treated by injection with a composition having up to 300 units, or more, of botulinum toxin type A and up to 300 units, or more, of botulinum toxin type E, in the dystonic neck muscles. After a few hours, the symptoms are substantially alleviated; i.e., the patient is able to hold his head and shoulder in a normal position.

Example 3

25

Use of Botulinum Toxin in the Treatment  
of Essential Tremor

30 A patient suffering from essential tremor, which is provoked by maintenance of posture or movement, is treated by injection with therapeutic amounts of botulinum toxin type A and botulinum toxin type B. After two weeks, the symptoms are substantially alleviated.

Example 3(a)

5           The method of Example 3 is repeated except that  
a patient suffering from essential tremor is injected  
with botulinum toxin type A and C. A similar result  
is obtained.

Example 3(b)

10           The method of Example 3 is repeated, except that  
a patient suffering from essential tremor is injected  
with botulinum toxin type A and D. A similar result  
is obtained.

15

Example 3(c)

          The method of Example 3 is repeated, except that  
a patient suffering from essential tremor is injected  
with botulinum toxin type A and E. A similar result  
20           is obtained.

Example 3(d)

25           The method of Example 3 is repeated, except that  
a patient suffering from essential tremor is injected  
with botulinum toxin type A and F. A similar result  
is obtained.

Example 3(e)

30

          The method of Example 3 is repeated, except that  
a patient suffering from essential tremor is injected  
with botulinum toxin type A and G. A similar result  
is obtained.

35



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Example 4Use of Botulinum Toxin in the Treatment  
of Spasmodic Dysphonia

5           A patient, unable to speak clearly due to spasm  
of the vocal chords, is treated by injection of  
therapeutic amounts of botulinum toxin type A and  
therapeutic amounts of botulinum toxin type B. After  
a few hours, the patient is able to speak clearly.

10

Example 4(a)

          The method of Example 4 is repeated except that  
a patient suffering from spasmodic dysphonia is  
15       injected with botulinum toxin type A and C. A similar  
result is obtained.

Example 4(b)

20           The method of Example 4 is repeated, except that  
a patient suffering from spasmodic dysphonia is  
injected with botulinum toxin type A and D. A similar  
result is obtained.

25

Example 4(c)

          The method of Example 4 is repeated, except that  
a patient suffering from spasmodic dysphonia is  
injected with botulinum toxin type A and E. A similar  
30       result is obtained.

Example 4(d)

          The method of Example 4 is repeated, except that  
35       a patient suffering from spasmodic dysphonia is

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injected with botulinum toxin type A and F. A similar result is obtained.

Example 4(e)

5           The method of Example 4 is repeated, except that a patient suffering from spasmodic dysphonia is injected with botulinum toxin type A and G. A similar result is obtained.

10                   Example 5

Use of Botulinum Toxin in the Treatment  
                  of Hemifacial Spasm

15           A patient is suffering from hemifacial spasm as manifested by involuntary rapid synchronous contraction of muscles innervated by the facial nerve on one side. The symptoms are sufficiently advanced to show not only contraction of the muscles around the eye,  
20           but twitches spread to involve the other ipsilateral facial muscles. The patient is injected with up to 300 units of botulinum toxin type A and up to 300 units of botulinum toxin type B, and after a few hours, the symptoms are substantially alleviated.

25                   Example 5(a)

                  The method of Example 5 is repeated except that a patient suffering from hemifacial spasm is injected  
30           with botulinum toxin type A and C. A similar result is obtained.

Example 5(b)

5 The method of Example 5 is repeated, except that a patient suffering from hemifacial spasm is injected with botulinum toxin type A and D. A similar result is obtained.

Example 5(c)

10 The method of Example 5 is repeated, except that a patient suffering from hemifacial spasm is injected with botulinum toxin type A and E. A similar result is obtained.

15

Example 5(d)

20 The method of Example 5 is repeated, except that a patient suffering from hemifacial spasm is injected with botulinum toxin type A and F. A similar result is obtained.

Example 5(e)

25 The method of Example 5 is repeated, except that a patient suffering from hemifacial spasm is injected with botulinum toxin type A and G. A similar result is obtained.

Example 6

30

Use of Botulinum Toxin in the Treatment  
of Blepharospasm

35 A 60-year old woman suffering from idiopathic blepharospasm, a focal form of dystonia involving the orbicularis oculi muscles and producing involuntary

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eye closure, is treated by injection with a therapeutic amount of botulinum toxin type A and type B into the orbicularis oculi muscle. A total of eight injections, both laterally and medially at the junction of the orbital and preseptal orbicularis is made. Twice as much of the solution is injected laterally as medially. Within twelve to twenty-four hours, detectable muscle weakness begins. Clinical improvement shows in two to three days. The involuntary blinking ceases. The effect of the injections lasts for 75 days.

Example 6(a)

The method of Example 6 is repeated except that a patient suffering from idiopathic blepharospasm is injected with botulinum toxin type A and C. A similar result is obtained.

Example 6(b)

The method of Example 6 is repeated, except that a patient suffering from idiopathic blepharospasm is injected with botulinum toxin type A and D. A similar result is obtained.

Example 6(c)

The method of Example 6 is repeated, except that a patient suffering from idiopathic blepharospasm is injected with botulinum toxin type A and E. A similar result is obtained.

Example 6(d)

5       The method of Example 6 is repeated, except that a patient suffering from idiopathic blepharospasm is injected with botulinum toxin type A and F. A similar result is obtained.

Example 6(e)

10       The method of Example 6 is repeated, except that a patient suffering from idiopathic blepharospasm is injected with botulinum toxin type A and G. A similar result is obtained.

15       Although there has been hereinabove described a use of multiple botulinum toxins for treating neuromuscular disorders and conditions in accordance with the present invention, for the purpose of illustrating the manner in which the invention may be  
20       used to advantage, it should be appreciated that the invention is not limited thereto since many obvious modifications can be made, and it is intended to include within this invention any such modifications as will fall within the scope of the appended claims.  
25       Accordingly, any and all modifications, variations, or equivalent arrangements which may occur to those skilled in the art, should be considered to be within the scope of the present invention as defined in the appended claims.

30

## WHAT IS CLAIMED IS:

1. A method of treating a patient suffering from a neuromuscular disorder or condition, said method comprising administering to the patient a therapeutically effective amount of a combination of at least two neurotoxins selected from a group consisting of botulinum toxin types A, B, C, D, E, F and G, an amount of each selected neurotoxin being further selected to control a duration of therapeutic activity of the administered combination.
2. The method according to claim 1 wherein the selected neurotoxins are botulinum toxin types A and B.
3. The method according to claim 1 wherein the selected neurotoxins are botulinum toxin types A and C.
4. The method according to claim 1 wherein the selected neurotoxins are botulinum toxin types A and D.
5. The method according to claim 1 wherein the selected neurotoxins are botulinum toxin types A and E.
6. The method according to claim 1 wherein the selected neurotoxins are botulinum toxin types A and F.
7. The method according to claim 1 wherein the selected neurotoxins are botulinum toxin types A and G.

5 8. The method according to claim 1 wherein the duration of therapeutic activity is suitable for treatment of joint dislocations, relaxation for physical therapy, alleviation of muscle spasm, immobilization of a joint undergoing surgery and for prevent of muscle contractions prior to or after surgery.

9. The method according to claim 1 wherein the duration of therapeutic activity is suitable for treating tendon and ligament alignment repair, treatment of scoliosis and spasm of sphincter muscles.

5 10. A method of treating a patient suffering from a neuromuscular disorder or condition, said method comprising administering to the patient a therapeutically effective amount of botulinum toxin type A and after a period of time administering to the patient a therapeutically effective amount of at least one neurotoxin selected from a group consisting of botulinum toxin types B, C, D, E, F and G in order to provide a short term enhancement of the therapeutic effect of the botulinum toxins.

10

11. The method according to claim 10 wherein the selected neurotoxin comprises botulinum toxin type B.

12. The method according to claim 10 wherein the selected neurotoxin comprises botulinum toxin type C.

13. The method according to claim 10 wherein the selected neurotoxin comprises botulinum toxin type D.

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14. The method according to claim 10 wherein the selected neurotoxin comprises botulinum toxin type E.

15. The method according to claim 10 wherein the selected neurotoxin comprises botulinum toxin type F.

16. The method according to claim 10 wherein the selected neurotoxin comprises botulinum toxin type G.

5 17. A composition suitable for treating a patient suffering from a neuromuscular disorder or condition, said composition comprising a therapeutically effective amount of a combination of at least two neurotoxins selected from a group consisting of botulinum toxin types A, B, C, D, E, F and G, an amount of each selected neurotoxin being further selected to control a duration of therapeutic activity of the administered combination.

18. The composition according to claim 17 wherein the selected neurotoxins are botulinum toxin types A and B.

19. The composition according to claim 17 wherein the selected neurotoxins are botulinum toxin types A and C.

20. The composition according to claim 17 wherein the selected neurotoxins are botulinum toxin types A and D.

21. The composition according to claim 17 wherein the selected neurotoxins are botulinum toxin types A and E.



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22. The composition according to claim 17 wherein the selected neurotoxins are botulinum toxin types A and F.

23. The composition according to claim 17 wherein the selected neurotoxins are botulinum toxin types A and G.

24. The composition according to claim 17 wherein the duration of therapeutic activity is suitable for treatment of joint dislocations, relaxation for physical therapy, alleviation of muscle spasm, immobilization of a joint undergoing surgery and for prevent of muscle contractions prior to or after surgery.

25. The composition according to claim 17 wherein the duration of therapeutic activity is suitable for treating tendon and ligament alignment repair, treatment of scoliosis and spasm of sphincter muscles.

## INTERNATIONAL SEARCH REPORT

Intern. Application No  
PCT/US 94/06418A. CLASSIFICATION OF SUBJECT MATTER  
IPC 5 A61K37/02

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 5 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,93 05800 (ALLERGAN) 1 April 1993 see the whole document, specially page 12, par. 4 ---	1-25
X	MICROBIOLOGICAL REVIEW, vol.56, no.1, March 1992, WASHINGTON, DC pages 80 - 99 SCHANTZ ET AL. 'Properties and Use of Botulinum Toxin and Other Microbial Neurotoxins in Medicine' see the whole document and specially page 93, right column --- -/--	1-25

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*A\* document member of the same patent family

Date of the actual completion of the international search

22 September 1994

Date of mailing of the international search report

18. 10. 94

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## INTERNATIONAL SEARCH REPORT

Internal Application No.

PCT/US 94/06418

## C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

[illegible]

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 94/06418

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 1-16 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compound/composition
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 94/06418

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9305800	01-04-93	AU-A- 2566492	27-04-93
		CA-A- 2119562	01-04-93
		EP-A- 0605501	13-07-94
WO-A-9400481	06-01-94	AU-B- 4646393	24-01-94

